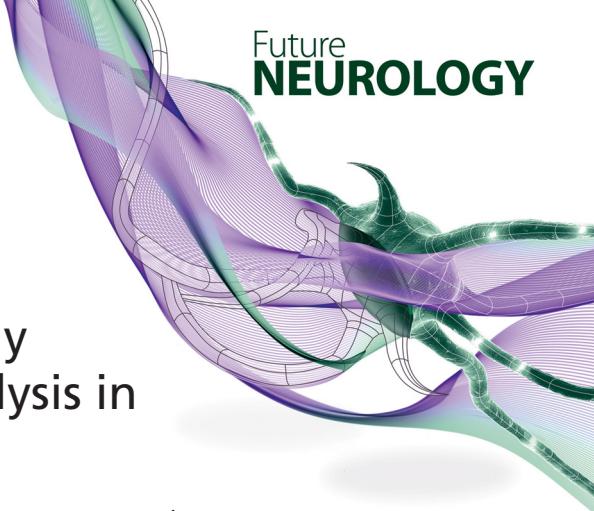


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Prehospital notification can effectively reduce in-hospital delay for thrombolysis in acute stroke

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Aim: To reduce in-hospital intervals by developing a prehospital notification (PHN) protocol which directly notifies a neurologist to prepare for possible treatment. **Methods:** A 24/7 connection was established between emergency medical services dispatch and the on-call neurologist. A database of all patients with in-hospital stroke code activation was developed, door-to-computed tomography (CT) time and door-to-needle time was recorded from January 2013 to December 2016. The statistical results were considered significant at $p < 0.05$. **Result:** PHN resulted in a significant reduction in door-to-CT time (median 14 vs 20; $p < 0.001$). Among patients who were treated with intravenous thrombolysis, door-to-needle time was significantly shorter in patients with PHN compared with non-PHN group (median 42 vs 70; $p < 0.001$). **Conclusion:** PHN effectively reduced door-to-CT and door-to-needle times.

First draft submitted: 24 October 2017; Accepted for publication: 4 December 2017; Published online: 17 January 2018

Keywords: door-to-CT • door-to-needle • golden hour • in-hospital delay • prehospital notification • stroke • stroke code • stroke outcome • symptom onset • thrombolysis

Stroke is a major cause of mortality and morbidity [1]. Intravenous tissue plasminogen activator (IV-tPA) remains a major available treatment option for acute stroke in developing countries where other methods such as thrombectomy are limited [2]. However, it has been proven to reduce the combined end point of death and disability after stroke if given within the golden hour after the onset of symptoms [3,4]. Its benefit is strongly time dependent [5] and multiple studies have shown that earlier treatment is associated with better outcomes [6–8]. Consensus guidelines recommend a target time of <25 min from hospital arrival to CT scan and <60 min from hospital arrival to treatment [9]. Unfortunately, due to significant delay in assessment of stroke patients in developing countries, the golden hour is often missed and patients lose the opportunity to be treated promptly [2].

There are numerous contributing factors to delay treatment of stroke. These can be divided into ‘out of hospital’ and ‘in-hospital’ delays and since decades ago, lots of studies have been conducted to evaluate such delays and therefore improving the outcome of stroke. Review of these studies shows that over time there has been a steady reduction in such time intervals [10].

Although major delays happen in the recognition of symptoms and transferring the patients to hospitals, In-hospital delays are also important in overall treatment failure. Multiple factors have been identified for in-hospital delays including decision making process, laboratory tests, neurology service arrival and imaging [10–12]. Previously, we tried to identify and resolve the issues related to in-hospital latencies in our hospital in Tabriz, Iran. We successfully implemented simple and effective methods to enhance in-hospital efficacy for timely management of acute stroke [2].

One simple and cost-effective measure to tackle in-hospital delay is prehospital notification (PHN) by the emergency medical services (EMS), which allows faster activation of the stroke team and has shown to be effective in reducing in-hospital delays [13–15].

Prenotification by contacting a neurologist directly, has been less studied [13,14,16]. The aim of this study was to compare in-hospital time intervals in stroke patients treated with IV-tPA with and without PHN.

Methods

Setting

Before commencing the study, the EMS personnel were trained for PHN of stroke patients. This study was retrospectively conducted with prospectively collected data from January 2013 (after establishment of the protocol) to December 2016 at Imam Reza Hospital in the city of Tabriz, Iran. During this period, all patients for whom the stroke code was activated were included in the study and patients were divided into two groups, with PHN and without PHN.

This hospital is a tertiary university center with an annual stroke admission of 900 patients, located in Tabriz in the province of East Azerbaijan, a city with an area of 45,700 km² and a population of 3.7 million (2011 census). The hospital is the only center in the province which provides 24/7 neurological services for thrombolysis. Endovascular treatment for acute stroke is not available in this center and none of the patients underwent thrombectomy or intra-arterial thrombolysis.

Protocol for PHN

The PHN protocol was established in December 2012. For this protocol, EMS personnel were initially trained. Once EMS personnel visit a patient with signs of probable stroke according to the Cincinnati stroke scale, where the onset of symptoms is less than 3 h, they notify EMS dispatch. The dispatch then directly contacts the on-call stroke neurologist, who is available 24/7 by mobile phone. The neurologist activates the hospital's stroke code by contacting the neurology resident and emergency physician at the hospital.

For all the patients, the stroke code was activated either before hospital arrival (PHN) or upon/after emergency department (ED) arrival (no-PHN). The patients in the 'no-PHN' group were those who were mainly transferred to hospital by family members or relatives. The in-hospital process after stroke code activation has been detailed elsewhere [2]. In all the cases, the imaging used for evaluation was a CT scan.

EMS training

All EMS and dispatch personnel were divided into three groups based on work shifts. Each group attended a 1-h training session lectured by a stroke neurologist. The importance of timing for early treatment of stroke patients was strongly emphasized to create a sense of urgency for treatment of these patients. The signs and symptoms of stroke according to the Cincinnati stroke scale were discussed. These training courses were repeated every 6 months.

Study purpose

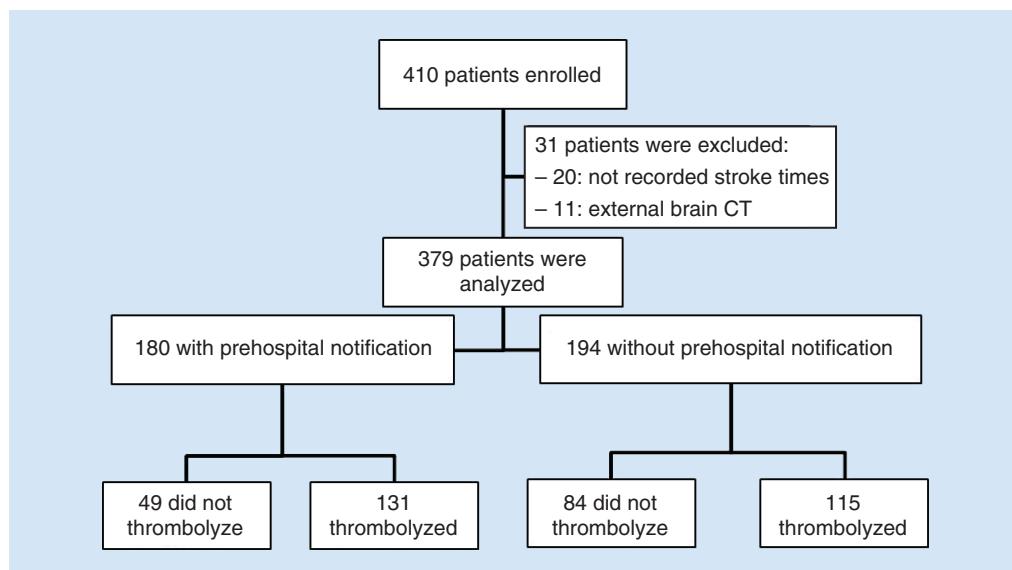
The primary purpose of the study was to: determine the difference of door-to-CT time for patients with and without PHN; and to determine the difference of door-to-needle time for patients with and without PHN (in case of IV thrombolysis).

Study variables

The data were recorded for all patients prospectively for demographics (age and gender), interval of symptom onset to hospital arrival time and door-to-CT time. For patients who were treated with a thrombolytic agent, door-to-needle time and baseline stroke severity as assessed by the National Institutes of Health Stroke Scale (NIHSS) was also recorded.

Statistical analysis

Statistical analysis was performed using SPSS version 21 (for Windows). Chi-square or the Fisher Exact tests were used for categorical variables. Because of the non-normal distribution of continuous variables, the Mann–Whitney U test was carried out. The statistical test results were considered significant at $p < 0.05$. The data were presented as median and interquartile range.

**Figure 1.** Distribution of participants.**Table 1.** Baseline characteristics of intravenous r-tissue plasminogen activator treated patients regarding prehospital notification status.

Characteristics	Prehospital notification		p-value
	Yes (n = 131)	No (n = 115)	
Age, years and median (IQR)	67 (58–75)	66 (55–77)	0.274
Male, n (%)	66 (57.4%)	72 (55.0%)	0.702
Baseline National Institutes of Health Stroke Scale, median (IQR)	15 (10–20)	11 (7.5–17)	<0.001
Onset to emergency department arrival time (min)	83 (55–121)	78 (50–120)	0.462
Door-to-CT time, min and median (IQR)	15 (10–25)	25 (18–45)	<0.001
Door-to-needle time, min, median (IQR)	42 (34–56)	70 (53–95)	<0.001

CT: Computed tomography; IQR: Interquartile range.

Ethics

This study was approved by the Regional Ethics Committee of Tabriz University of Medical Sciences. Informed consent was obtained from participants or their next of kin.

Results

During the study period, the ED was notified of a total of 410 patients for which the stroke code was activated (with or without PHN). Three patients were transferred to the hospital by helicopter EMS. Of the 410 patients, 31 were excluded. The stroke timings were not recorded for 20 patients and 11 patients had brain imaging performed elsewhere before hospital arrival. The analysis was carried out for the remaining 379 patients, 180 with PHN and 199 without PHN (Figure 1).

Median door-to-CT time for the PHN group was 6 min less than for the no-PHN group, which was statistically significant (median [interquartile range: IQR]; 14 [9–22] vs 20 [14–35]; p < 0.001).

Overall, 64.9% (246/379) of all patients were treated with IV thrombolysis (IVT). Table 1 shows baseline characteristics of patients treated with IV recombinant tissue plasminogen activator (r-TPA) associated with PHN. Among patients treated with IVT, the median door-to-CT and door-to-needle time was significantly lower for the PHN group compared with those in the no-PHN group (median [IQR]; 15 [10–22] vs 25 [18–45]; p < 0.001 and median [IQR]; 42 [34–56] vs 70 [53–95]; p < 0.001, respectively). Of all treated with thrombolysis, 17 (13%) in PHN and 35 (30%) in non-PHN had a symptom onset of more than 3 h.

This study also evaluated the accuracy of code activation by EMS technicians. The EMS technicians were instructed based on the protocol to notify dispatch if they were visiting a patient who met the Cincinnati stroke

Table 2. Rationale for not administrating intravenous thrombolysis.

Contraindication	Prehospital notification		Total
	No	Yes	
Intracranial hemorrhage	14	14	28
Minor stroke	5	1	6
Transient ischemic attack or rapidly improving	12	4	16
Large stroke (more than a third)	2	1	3
Awakening stroke	8	6	14
Patients refused treatment	6	2	8
Nonstroke diagnosis	6	7	6
International normalized ratio >1.7	2	0	2
Symptom onset > out of treatment window	11	6	17
Refractory hypertension	1	3	4
Age >80	10	4	14
Medication not available	1	0	1
Active gastrointestinal bleeding	1	0	1
Recent myocardial infarction	1	1	2
Recent stroke	1	0	1
3–4.5 h and National Institutes of Health Stroke Scale >25	1	0	1
Intraparenchymal mass	2	0	2
Total	84	49	133
Onset to treatment time was more than 3 or 4.5 h based on the latest guideline.			

scale and the onset of symptoms or the time the patient was last known to be normal was less than 3 h. The code activation was correct in 89.4% (161/180) of patients. Among the remaining 19 (10.6%) patients, six had actual onset times more than what was recommended in guidelines, six had experienced stroke on awakening and the code was activated for seven patients based on items that were not part of the Cincinnati stroke scale (generalized weakness, loss of consciousness and dizziness, etc.). Table 2 shows the contraindications for administering IVT in both groups. Based on recent guidelines [9,17], IVT is not recommended in patients presenting in 3–4.5 h window and with a severe stroke (NIHSS >25). As a result, thrombolysis was not given to one patient who fell into this category in no-PMH group.

Discussion

This study demonstrates that educating EMS personnel and implementing PHN with a direct 24/7 telephone hotline between the EMS dispatch and a neurologist reduced door-to-CT and door-to-needle times for acute stroke patients. Previous studies have reported similar results about the effect of PHN on in-hospital time targets [18–25].

The ED of Imam Reza Hospital is very crowded because it is the only referral center in the province for acute vascular patients, trauma and other emergencies. The advantage of the protocol used in this study was the direct contact between EMS and the on-call neurologist who is responsible for notifying the CT room, lab center and stroke unit. This decreased the load on the ED physician, who is routinely overburdened with emergency referrals. Furthermore, since the attending neurologist is involved from the beginning, the stroke unit has more time to get prepared before patient arrival and even more time available to transfer a patient, if necessary.

Based on stroke registry (established in 2015) data in our hospital, annual number of stroke admission is about 900 patients. Nevertheless, more than 410 patients were treated with IVT during a 4-year period. The reason for the huge gap between the total admission and stroke code activation is the majority of admitted patients present after the 'golden hour' for thrombolysis due to out of hospital delays. It is notable that a recent study at the center found that only 31% of patients with acute stroke arrived at the ED within 3 h of symptom onset [26]. Although implementation of the stroke code system and PHN are important interventions to reduce onset to treatment time, the severe lack of public awareness to recognize stroke symptoms is the reason why thrombolysis rate does not rise effectively. In a recent report, the rate of thrombolysis for acute stroke patients was less than 5% at this center [27]; therefore, public education is crucial to reach a higher rate of thrombolysis.

Response to IVT is time dependent and its effect on a good outcome is negatively influenced by treatment delay [28]. Based on the data from hospitals participating in the Get With the Guidelines-Stroke Program, among 25,504 patients treated with IVT, every 15 min reduction in door-to-needle time was associated with 5% lower odds of mortality [29]. So by implementing PHN system and reducing the door-to-needle time, the probability of a good outcome could be increased.

For hospitals with stroke centers that have not yet implemented the PHN system, we strongly suggest to do so, because its implementation is easy and cheap, it does not need any specific infrastructure and its effects reflect in the short term.

Overall, PHN by EMS was correct for 89% of patients, which indicated that the 1-h training sessions every 6 months for EMS personnel was efficient, but in 19 patients, the EMS incorrectly prenotified dispatch hence the trainers should emphasize on the importance of taking more detailed history for precise determination of symptoms onset.

It is very important to note that stroke severity plays an important role in ‘prehospital delays’ or ‘symptom onset to seek medical help’ times [30]. As mentioned before, the aim of this study was not to evaluate such delays, but to reduce the ‘in-hospital time’ intervals. Moreover, we did not consider stroke risk factors as these may have little impact on our variables.

In a study by Sauser *et al.*, the door-to-imaging time was reduced 0.31 min per NIHSS score, but they could not demonstrate any significant relation between door-to-needle time and severity [31]. In a multicenter study involving 5563 patients, stroke severity was directly associated with thrombolysis delay. However, in this study, PHN was not considered and patients were included from a stroke registry regardless of their method of arrival and any PHN [32]. It seems that PMH can reduce in-hospital delay as the neurologist will arrange for prompt imaging, laboratory tests and an imminent thrombolysis therefore ‘stroke severity’ appears to have a limited role in such setting. However, we agree that stroke severity can affect intervals in ‘no-PHN’ group.

This study had some limitations. First, it was carried out at a single center with a limited number of cases; the results may not be applicable to other health systems. More broad multicenter research is necessary to validate the results and determine whether shortening of the door-to-needle time by PHN lead to better outcomes for the patients. Second, the staffs were aware of eligible patients who presented with stroke symptoms within the 3-h window but EMS personnel missed for notification, but specific data are not available for these patients. Third, the total number of stroke admission, the stroke code and temporal windows rate are not available for this study, but Tabriz stroke registry program is running since 1 January 2015 and we have more detailed data since then.

Conclusion

The results of this study show that simple, brief and continuing training sessions for EMS personnel and implementation of PHN by direct 24/7 telephone contact between dispatch and a neurologist effectively reduced door-to-CT and door-to-needle times for acute stroke patients.

Summary points

- The aim was to study the effect of prehospital notification (PHN) on in-hospital time interval and to improve the stroke management outcome in developing countries.
- The emergency medical services (EMS) personnel were trained before starting the study.
- A 24/7 phone line connection was established between EMS and the on-call neurologist.
- All data recorded between 2013 and 2016 were reviewed.
- The analysis was carried out for 379 patients, 180 with PHN and 199 without PHN.
- PHN by EMS, resulted in a significant reduction in door-to-CT time.
- Door-to-needle time was significantly shorter in patients with PHN.
- The code activation by EMS was correct in 89.4% (161/180) of patients.

Financial & competing interests disclosure

This research was supported by Neuroscience Research Center (NSRC), Tabriz University of Medical Science. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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